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Endopeptidases 3.4.24.15 and 24.16 in endothelial cells: potential role in vasoactive peptide metabolism.

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The closely related metalloendopeptidases EC (EP24.15; thimet oligopeptidase) and 24.16 (EP24.16; neurolysin) cleave a number of vasoactive peptides such as bradykinin and neurotensin in vitro. We have previously shown that hypotensive responses to bradykinin are potentiated by an inhibitor of EP24.15 and EP24.16 (26), suggesting a role for one or both enzymes in bradykinin metabolism in vivo. In this study, we have used selective inhibitors that can distinguish between EP24.15 and EP24.16 to determine their activity in cultured endothelial cells (the transformed human umbilical vein endothelial hybrid cell line EA.hy926 or ovine aortic endothelial cells). Endopeptidase activity was assessed using a specific quenched fluorescent substrate [7-methoxycoumarin-4-acetyl-Pro-Leu-Gly-d-Lys(2,4-dinitrophenyl)], as well as the peptide substrates bradykinin and neurotensin (assessed by high-performance liquid chromatography with mass spectroscopic detection). Our results indicate that both peptidases are present in endothelial cells; however, EP24.16 contributes significantly more to substrate cleavage by both cytosolic and membrane preparations, as well as intact cells, than EP24.15. These findings, when coupled with previous observations in vivo, suggest that EP24.16 activity in vascular endothelial cells may play an important role in the degradation of bradykinin and/or other peptides in the circulation.

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